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Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number:

**0 459 568 A2**

(12)

**EUROPEAN PATENT APPLICATION**(21) Application number: **91201226.7**

(51) Int. Cl.<sup>5</sup>: **A61K 31/41**, A61K 31/44,  
A61K 31/445, A61K 31/55,  
C07D 413/04, C07D 453/02,  
C07D 471/08, C07D 487/08

(22) Date of filing: **22.05.91**

(30) Priority: **31.05.90 GB 9012173**  
**26.11.90 GB 9025661**

(43) Date of publication of application:  
**04.12.91 Bulletin 91/49**

(84) Designated Contracting States:  
**CH DE FR GB IT LI NL**

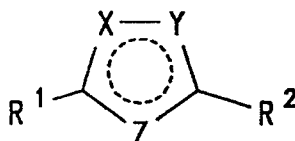
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(54) **Substituted oxadiazoles and thiadiazoles for use in the treatment of glaucoma and novel compounds having such use.**

(57) The use of compounds for formula (I):

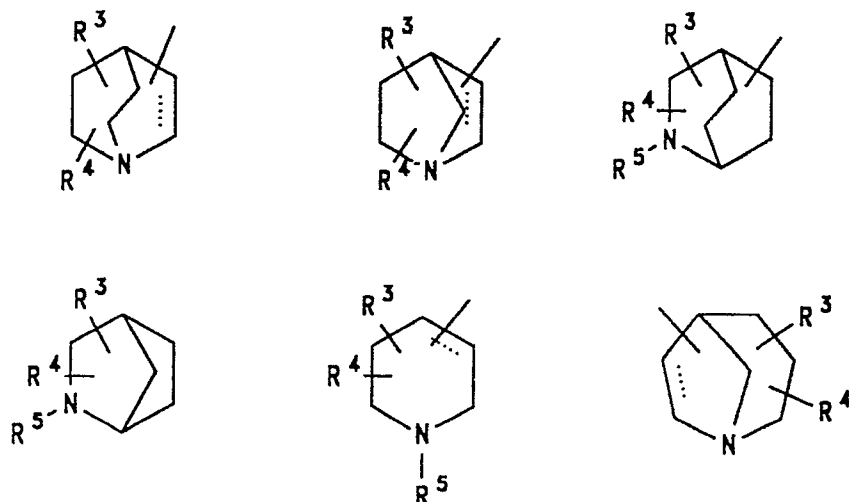


( I )

or a salt or prodrug thereof; wherein one of X, Y, or Z is an oxygen or sulphur atom and the other two are nitrogen atoms, and the dotted circle represents two double bonds thus forming a 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole or 1,2,4-thiadiazole nucleus;

R<sup>1</sup> represents a non-aromatic azacyclic or azabicyclic ring system selected from

**EP 0 459 568 A2**



wherein the broken line represents an optional chemical bond;

the substituents R<sup>3</sup> and R<sup>4</sup> may be present at any position, including the point of attachment to the oxa- or thia-diazole ring, and independently represent hydrogen, C<sub>1-4</sub> alkyl, halo, C<sub>1-4</sub> alkoxy, hydroxy or carboxy, or R<sup>3</sup> and R<sup>4</sup> together represent carbonyl;

the group R<sup>5</sup> represents hydrogen or C<sub>1-4</sub> alkyl; and

R<sup>2</sup> represents hydrogen, C<sub>1-8</sub> alkyl optionally substituted by hydroxy or fluoro, C<sub>2-8</sub> alkenyl, OR<sup>7</sup>, SR<sup>7</sup>, NR<sup>7</sup>R<sup>8</sup>, CN, CO<sub>2</sub>R<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup> OR NHCONHR<sup>9</sup> where R<sup>9</sup> is C<sub>1-4</sub> alkyl; wherein R<sup>7</sup> and R<sup>8</sup> independently represent hydrogen or saturated or unsaturated C<sub>1-4</sub> alkyl provided that, when R<sup>7</sup> and R<sup>8</sup> in NR<sup>7</sup>R<sup>8</sup> are both hydrogen, at least one of R<sup>3</sup> and R<sup>4</sup> is C<sub>1-4</sub> alkyl,

in the treatment of glaucoma, novel compounds having such use, formulations containing them and their synthesis.

The present invention relates to a class of substituted oxadiazoles and thiadiazoles for use in the treatment of glaucoma and to certain novel compounds having such use, formulations containing them and their synthesis.

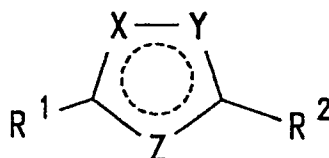
Glaucoma is an ocular disorder associated with elevated intraocular pressures which are too high for normal function and may result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e. the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by many ophthalmologists to represent the earliest phase of glaucoma.

Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. Topical administration to the eye of agents such as pilocarpine may be used in order to improve the outflow of aqueous humour and reduce the intraocular pressure (see Drugs, 1979, vol 17, 38 and Drugs and Ther. Bull., 1989, vol 21, 85), but these have associated side effects such as emesis and myosis.

We have now found compounds which lower the intraocular pressure without exhibiting side effects to the extent associated with hitherto-known drugs used against glaucoma which act through cholinergic mechanisms.

European patent specifications nos. EP-A-239309, EP-A-301729, EP-A-307142, EP-A-307140, EP-A-323864 and EP-A-322034 describe classes of compounds useful in the treatment of certain neurological and mental illnesses such as Alzheimer's disease. These classes include compounds which are an oxadiazole or thiadiazole, or a salt or prodrug thereof, which is substituted on one of the ring carbon atoms with a non-aromatic azacyclic or azabicyclic ring and substituted on the other ring carbon atom with a substituent of low lipophilicity or a hydrocarbon substituent. We have found that a subclass of these compounds effects reduction of intraocular pressure without exhibiting severe adverse effects on pupil size.

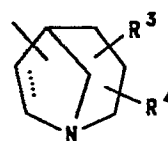
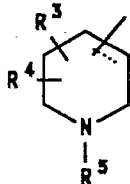
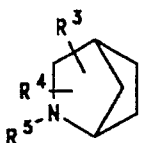
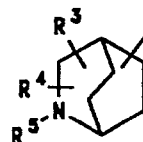
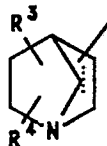
The compounds for use according to the present invention may be represented by structural formula (I):



( I )

or a salt or prodrug thereof; wherein one of X, Y, or Z is an oxygen or sulphur atom and the other two are nitrogen atoms, and the dotted circle represents two double bonds thus forming a 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole or 1,2,4-thiadiazole nucleus;

R<sup>1</sup> represents a non-aromatic azacyclic or azabicyclic ring system selected from



wherein the broken line represents an optional chemical bond;

the substituents  $R^3$  and  $R^4$  may be present at any position, including the point of attachment to the oxa- or thia-diazole ring, and independently represent hydrogen,  $C_{1-4}$  alkyl, halo,  $C_{1-4}$  alkoxy, hydroxy or carboxy, or  $R^3$  and  $R^4$  together represent carbonyl;

5 the group  $R^5$  represents hydrogen or  $C_{1-4}$  alkyl; and

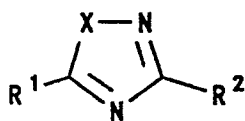
$R^2$  represents hydrogen,  $C_{1-8}$  alkyl optionally substituted by hydroxy or fluoro,  $C_{2-8}$  alkenyl,  $OR^7$ ,  $SR^7$ ,  $NR^7R^8$ ,  $CN$ ,  $CO_2R^7$ ,  $CONR^7R^8$  OR  $NHCONHR^9$  where  $R^9$  is  $C_{1-4}$  alkyl; wherein  $R^7$  and  $R^8$  independently represent hydrogen or saturated or unsaturated  $C_{1-8}$  alkyl provided that, when  $R^7$  and  $R^8$  in  $NR^7R^8$  are both hydrogen, at least one of  $R^3$  and  $R^4$  is  $C_{1-4}$  alkyl.

10 In the definition of  $R^1$ , it will be appreciated that the nitrogen atom in the azacyclic or azabicyclic ring system will carry a lone pair of electrons.

In the definition of  $R^2$ , unless otherwise specified, "alkyl" and "alkenyl" groups may be straight, branched or cyclic groups.

One subclass of compounds within the scope of the present invention is represented by formula (II):

15



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( II )

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wherein  $R^1$ ,  $R^2$  and  $X$  are as defined above, and salts and prodrugs thereof.

Preferably,  $R^1$  is 1,2,5,6-tetrahydropyridyl (optionally substituted on the ring nitrogen with methyl or ethyl), 1-azabicyclo[2.2.1]heptanyl or 2-azabicyclo[2.2.2]octanyl (isoquinuclidinyl). Also preferred is quinuclidinyl.

30 Preferably,  $R^3$  and  $R^4$  are selected from hydrogen, hydroxy and  $C_{1-4}$  alkyl groups. Especially preferred is when  $R^3$  is hydrogen or methyl and  $R^4$  is hydrogen.

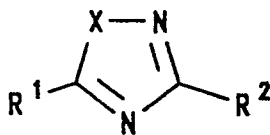
Preferably, the group  $R^5$  represents hydrogen, methyl or ethyl.

Preferably,  $R^2$  is  $C_{1-8}$  alkyl, more preferably  $C_{1-3}$  alkyl, optionally substituted by OH or F, or  $NR^7R^8$  when  $R^7$  is hydrogen, or saturated or unsaturated  $C_{1-3}$  alkyl, and  $R^8$  is saturated or unsaturated  $C_{1-3}$  alkyl. Especially preferred is when  $R^2$  is methyl, ethyl, cyclopropyl, methylamino, dimethylamino or dipropargylamino ( $-N(CH_2C\equiv CH)_2$ ).

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Another subclass of compounds within the scope of the present invention is represented by formula (III):

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( III )

50 or a salt or prodrug thereof, wherein  $R^1$  is 1,2,5,6-tetrahydropyridyl (optionally substituted on the ring nitrogen with methyl or ethyl), 1-azabicyclo [2.2.1]heptanyl, 2-azabicyclo[2.2.2]octanyl (isoquinuclidinyl), quinuclidinyl or piperidyl;

$R^3$  and  $R^4$  are selected from hydrogen, hydroxy and  $C_{1-4}$  alkyl (preferred is when  $R^3$  is hydrogen);

$R^5$  is hydrogen, methyl or ethyl;

55  $R^2$  is  $C_{1-8}$  alkyl, preferably  $C_{1-5}$  alkyl, optionally substituted by OH or F,  $C_{2-8}$  alkenyl, preferably ethenyl,  $NR^7R^8$  or  $CONR^7R^8$  when  $R^7$  is hydrogen, or saturated or unsaturated  $C_{1-3}$  alkyl, and  $R^8$  is hydrogen or saturated or unsaturated  $C_{1-3}$  alkyl, or  $NHCONHR^9$  where  $R^9$  is as defined above. Especially preferred is when  $R^2$  is methyl, ethyl, isopropyl, cyclopropyl, n- or sec- pentyl, ethenyl, methylamino,

dimethylamino, dipropargylamino,  $\text{CONH}_2$  or  $\text{NHCONH(tert-butyl)}$ .

Prodrugs of compounds of this invention have a substituent on the oxa- or thia-diazole ring which is convertible in vivo to a substituent as defined for  $\text{R}^2$ , such as a group hydrolysable in vivo to an amino group.

5 Groups which are hydrolysable in vivo to an amino group on the compounds of this invention may be readily ascertained by administering the compound to a human or animal and detecting, by conventional analytical techniques, the presence of the corresponding compound having an amino substituent in the urine of a human or animal. Examples of such groups include, for example, amido and urethane substituents, in particular a group of formula  $-\text{NH.Q}$ , wherein Q represents  $\text{CHO}$ ,  $\text{COR}$  or  $\text{CO}_2\text{R}$ , and R

10 represents an optionally substituted hydrocarbon group.  
In this context, the hydrocarbon group R includes groups having up to 20 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable groups R include  $\text{C}_{1-9}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{3-7}$  cycloalkyl( $\text{C}_{1-6}$ )alkyl, aryl, and aryl( $\text{C}_{1-6}$ )alkyl. The alkyl group R may be straight or branched chain and may contain, for example, up to 12 carbon atoms, suitably from 1 to 6

15 carbon atoms. In particular the group may be substituted methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, n- or iso-heptyl, or n- or iso-octyl. Suitable cycloalkyl groups include cyclopentyl and cyclohexyl. The aryl group R includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, substituent groups.

Most of the compounds of this invention have at least one asymmetric centre and often more than one; and can therefore exist as both enantiomers and diastereoisomers. In particular, those compounds possessing an unsymmetrical azabicyclic ring system may exist as exo and endo diastereoisomers. It is to be understood that the invention covers all such isomers and mixtures thereof.

Also included within the scope of the present invention are salts of the novel compounds. It will be appreciated that salts of the compounds for use in medicine will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or their non-toxic pharmaceutically acceptable salts. Acid addition salts, for example, may be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, oxalic, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, p-toluene sulphonic, carbonic acid or phosphoric acid. Preferred are the hydrochloride, hydrogen oxalate, maleate, tartrate and tosylate salts. Where the novel compound carries a carboxylic acid group the invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.

Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Such quaternary ammonium derivatives penetrate poorly into the central nervous system and are therefore useful as peripherally selective muscarinic agents, useful for example as antispasmodic agents, agents to reduce gastric acid secretion, agents to block the muscarinic actions of acetylcholinesterase inhibitors in the treatment of myasthenia gravis and as agents to co-administer with muscarinic agonists in Alzheimer's disease.

Examples of compounds for use according to this invention include:

40 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine;  
Exo-3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
3-(3-methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine;  
45 3-(3-dipropargylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-ethyl-1,2,5,6-tetrahydropyridine;  
3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
Exo-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
50 (-)-Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
Endo-3-(3-cyclopropyl-1,2,4-thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
Endo-3-(3-dimethylamino-1,2,4-thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane; and  
(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine;  
55 3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine;  
3-(3-methyl-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine;  
3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine;  
Exo-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane;

- Exo-3-(3-dimethylamino-1,2,4-thiadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane;  
 Exo-3-(3-isopropyl-1,2,4-thiadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane;  
 3-(3-carboxamido-1,2,4-oxadiazol-5-yl)quinuclidine;  
 Exo-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 5 3-(3-ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidine;  
 3-(3-*t*-butylaminocarbonylamino-1,2,4-oxadiazol-5-yl)quinuclidine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)quinuclidine;  
 Exo-3-(3-*n*-pentyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 10 Exo-3-(3-(3-methylbut-1-yl)-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 and salts and prodrugs thereof.

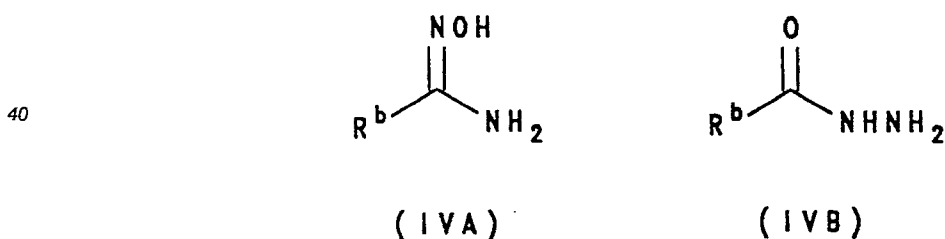
Some of the compounds having the use according to this invention are novel and therefore the present invention further provides:

- Exo-3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 15 3-(3-methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine;  
 3-(3-dipropargylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-ethyl-1,2,5,6-tetrahydropyridine;  
 20 Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
 (-)-Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
 3-(3-ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidine;  
 3-(3-*t*-butylaminocarbonylamino-1,2,4-oxadiazol-5-yl)quinuclidine;  
 25 3-(3-ethyl-1,2,4-oxadiazol-5-yl)quinuclidine hydrogen;  
 Exo-3-(3-*n*-pentyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 Exo-3-(3-(3-methylbut-1-yl)-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 and salts and prodrugs thereof.

- The compounds for use according to this invention including the novel compounds of the invention may  
 30 be prepared as described in the processes (A) to (J) below or by processes analogous to those known to  
 persons skilled in the art.

According to one general process (A) the compounds of this invention having an oxadiazole nucleus  
 may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of  
 formula  $R^a\text{-CO}_2\text{H}$ , with either a compound of formula (IVA) or (IVB) or a salt thereof:

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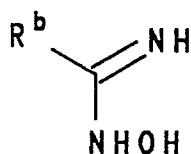
wherein one of  $R^a$  and  $R^b$  is  $R^1$ , and the other is  $R^2$ .

Suitable reactive derivatives of the acid  $R^a\text{-CO}_2\text{H}$  include esters, for example  $\text{C}_{1-4}$  alkyl esters, thio  
 esters, for example pyridylthioester, acid anhydrides, for example  $(R^a\text{CO})_2\text{O}$ , acid halides, for example the  
 acid chloride, orthoesters, and primary, secondary and tertiary amides.

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When the compound of formula (IVA) is employed the product of the reaction is a 1,2,4-oxadiazole. It  
 will be appreciated that the compound (IVA) can also be considered as the alternative tautomeric form:

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10 A 3-substituted-1,2,4-oxadiazole-5-yl compound is produced if  $R^a$  represents  $R^1$  and  $R^b$  in formula (IVA) represents  $R^2$ . In this case, a preferred reactive derivative of the acid  $R^a\text{-CO}_2\text{H}$  is a  $C_{1-4}$  alkyl ester. The reaction is conveniently carried out in tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol at about  $20^\circ\text{C}$  to  $100^\circ\text{C}$  for about 1 to 6 hours.

15 A 5-substituted-1,2,4-oxadiazol-3-yl compound is produced by the process of this invention when  $R^a$  represents  $R^2$  and  $R^b$  represents  $R^1$ . For this reaction a suitable reactive derivative is the acid chloride or the acid anhydride  $(R^a\text{CO})_2\text{O}$ . The reaction may be carried out by treating compound (IVA), in the cold, e.g. from about  $-5^\circ\text{C}$  to  $+10^\circ\text{C}$ , with the reactive derivative, followed by heating at about  $80^\circ\text{C}$  -  $120^\circ\text{C}$  for about 1 to 6 hours.

20 When the compound of formula (IVB) is employed, the product of the process of this invention is a 1,3,4-oxadiazole. In this case, a preferred reactive derivative of the acid  $R^a\text{CO}_2\text{H}$  is an orthoester of formula  $R^a\text{C(OR')}_3$  where  $R'$  represents  $C_{1-3}$  alkyl. The process is conveniently effected by heating the hydrazide (IVB) with the orthoester in a solvent such as methanol at reflux temperature for about 2 to 8 hours. An intermediate of formula :  $R^b\text{CO.NH.N=C(R}^a\text{)OR'}$ , may be isolated by evaporation of the solvent. The intermediate is then treated with a strong base such as potassium t-butoxide or 1,8-diazabicyclo [5.4.0] undec-7-ene, in butanol for about 10 to 24 hours at about  $90 - 150^\circ\text{C}$ .

25 The compounds of this invention having an oxadiazole nucleus may also be prepared by:

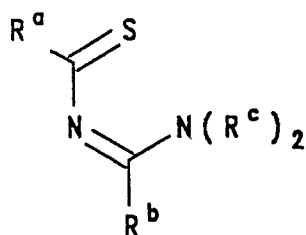
(B) reacting a compound of formula  $R^a\text{-CO-N=C(R}^b\text{)N(CH}_3\text{)}_2$ , with hydroxylamine;

(C) oxidizing an oxadiazoline with an oxidizing agent such as potassium permanganate, nitrogen dioxide, or N-bromosuccinimide; or

30 (D) when  $R^2$  is amino, reacting a compound of formula (IVA) with a cyanogen halide, such as cyanogen bromide.

The compounds of this invention having an thiadiazole nucleus may be prepared by:

(E) (for the preparation of 1,2,4-thiadiazoles), cyclisation of a compound of formula:



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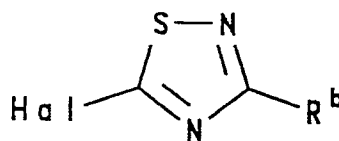
45 wherein one of  $R^a$  and  $R^b$  is a group  $R^1$ , and the other is a group  $R^2$ ; and  $R^c$  is hydrogen or an alkyl group.

Cyclisation can be achieved using an aminating agent such as hydroxylamine-O-sulphonic acid in a lower alkanol such as methanol, ethanol or propanol, in the presence of pyridine, at between  $-20^\circ\text{C}$  and  $50^\circ\text{C}$  for about 1-6 hours. When  $R^c$  is H, cyclisation may also be achieved by use of an oxidising agent such as bromine, iodine, hydrogen peroxide or nitric acid;

50 (F) (for the preparation of 1,2,4-thiadiazoles) cycloaddition of a nitrile sulphide  $R^a\text{-C}\equiv\text{N}^+\text{-S}^-$  with a nitrile of formula  $R^b\text{CN}$  where  $R^a$  and  $R^b$  are as defined above.

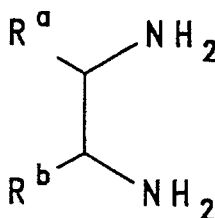
(G) (for the preparation of 1,2,4-thiadiazoles) reaction of a thiadiazole of formula:

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with a reagent which provides as anion  $\text{R}^{\text{a}}$ , where  $\text{R}^{\text{a}}$  and  $\text{R}^{\text{b}}$  are as previously defined and Hal represents halogen.

- 10 Reagents which may provide the anion  $\text{R}^{\text{a}}$  include a Grignard reagent  $\text{R}^{\text{a}}\text{MgY}$  (where  $\text{Y}$  = halogen); an organocuprate reagent such as  $\text{LiR}^{\text{a}}\text{Cu}$ ; an organolithium reagent  $\text{R}^{\text{a}}\text{Li}$ ; or a compound which stabilises the anion by means of an adjacent activating group such as an ester or enolisable ketone function. In this case, the adjacent ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.
- 15 (H) (for the preparation of 1,2,5-thiadiazoles) reaction of a diamine of the type



where  $\text{R}^{\text{a}}$  and  $\text{R}^{\text{b}}$  are as defined above, with a sulphur chloride such as thionyl chloride or sulphur dichloride.

- (J) (for the preparation of 1,3,4-thiadiazoles) dehydration of a thiosemicarbazide of formula  $\text{R}^{\text{x}}\text{CSNHNHCONR}^{\text{p}}\text{R}^{\text{q}}$  where  $\text{R}^{\text{x}}$  is an azacyclic or azabicyclic ring system and  $\text{R}^{\text{p}}$  and  $\text{R}^{\text{q}}$  are hydrogen or an alkyl group, with a dehydrating agent such as sulphuric acid, polyphosphoric acid or methanesulphonic acid.

The azacyclic or azabicyclic moiety may be introduced into the molecules concerned by methods known from the art, in particular by methods analogous to those described in EP-A-0239309.

- 35 In any of the above reactions it may be necessary and/or desirable to protect any sensitive groups in the compounds. For example, if  $\text{R}^{\text{a}}$  and/or  $\text{R}^{\text{b}}$  include amino, carboxy, hydroxy or thiol groups, these may be protected in conventional manner. Thus, suitable protecting groups for hydroxy groups include silyl groups such as trimethylsilyl or t-butyldimethylsilyl, and etherifying groups such as tetrahydropyranyl; and for amino groups include benzyloxycarbonyl and t-butoxycarbonyl. Carboxy groups are preferably protected
- 40 in a reduced form such as in the form of their corresponding protected alcohols, which may be subsequently oxidised to give the desired carboxy group. Thiol groups may be protected by disulphide formation, either with the thiol itself or with another thiol to form a mixed disulphide. The protecting groups may be removed at any convenient stage in the synthesis of the desired compound according to conventional techniques.

- 45 When administered for the treatment of elevated intraocular pressure or glaucoma, the active compound is preferably administered topically to the eye, although systemic treatment is, as indicated, also possible. The dose administered can be from as little as 0.1 to 25 mg or more per day, singly, or preferably on a 2 to 4 dose per day regimen although a single dose per day is satisfactory.

- 50 The present invention therefore also provides a pharmaceutical formulation suitable for use in reducing intraocular pressure or for treating glaucoma which formulation comprises a novel compound of formula (I) and a pharmaceutically acceptable carrier.

It will be understood that any formulation may further comprise another active ingredient such as another antiglaucoma agent for example a topical carbonic anhydrase inhibitor.

- 55 When given systemically, the drug can be given by any route, although the oral route is preferred. In oral administration, the drug can be employed in any of the usual dosage forms such as tablets or capsules, either in a contemporaneous delivery or sustained release form. Any number of the usual excipients or tableting aids can likewise be included. Further details of suitable formulations are given in the aforementioned European patent specifications.



When given by the topical route, the active compound or an ophthalmologically acceptable salt thereof such as the hydrochloride salt is formulated into an ophthalmic preparation. In such formulations, from 0.0005% to 15% by weight can be employed. The objective is to administer a dose of from 0.1 to 1.0 mg per eye per day to the patient, with treatment continuing so long as the condition persists.

Thus, in an ophthalmic solution, insert, ointment or suspension for topical delivery, or a tablet, intramuscular or intravenous composition for systemic delivery, the active medicament or an equivalent amount of a salt thereof is employed, the remainder being carrier, excipients, preservatives and the like as are customarily used in such compositions.

The active drugs of this invention are most suitably administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye such as a suspension, ointment, or as a solid insert. A preferred composition is eye drops. Formulations of these compounds may contain from 0.0005 to 15% and especially 0.05% to 2% of medicament. Higher dosages as, for example, about 10% or lower dosages can be employed provided the dose is effective in reducing or controlling elevated intraocular pressure. As a unit dosage from between 0.001 to 10.0 mg, preferably 0.005 to 2.0 mg, and especially 0.1 to 1.0 mg of the compound is generically applied to the human eye, generally on a daily basis in single or divided doses so long as the condition being treated exists.

This invention therefore further provides a pharmaceutical formulation adapted for topical administration to the eye which formulation comprises a compound of formula (I) and a carrier suitable for topical administration.

These hereinbefore described dosage values are believed accurate for human patients and are based on the known and presently understood pharmacology of the compounds, and the action of other similar entities in the human eye. As with all medications, dosage requirements are variable and must be individualized on the basis of the disease and the response of the patient.

For topical administration, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like.

The pharmaceutical formulation may also be in the form of a solid insert such as one which after dispensing the drug remains essentially intact, or a bio-erodible insert that is soluble in lacrimal fluids or otherwise disintegrates.

The present invention will now be illustrated by the following descriptions and examples:

#### DESCRIPTIONS

The following descriptions exemplify the preparation of compounds having the use according to the present invention:

Description A: 3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine hydrochloride

Prepared according to Example 3 of European patent specification no. 322 034.

Description B: 3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine hydrochloride

Prepared according to Example 6 of European patent specification no. 323 864.

Description C: Exo-3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane hydrochloride

Prepared according to Example 5 of European patent specification no. 323 864.

Description D: Endo-3-(3-Cyclopropyl-1,2,4-thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane hydrogen oxalate

5 Prepared according to Example 14 of European patent specification no. 307 142.

Description E: Endo-3-(3-Dimethylamino-1,2,4-thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane hydrogen oxalate

Prepared according to Example 11 of European patent specification no. 307 142.

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Description F: 3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine sesquioxalate

Prepared according to Example 6 of European Patent specification No. 322 034.

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Description G: 3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine hydrogen oxalate

Prepared according to Example 5 of European Patent specification No. 322 034.

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Description H: 3-(3-Methyl-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine hydrochloride

Prepared according to Example 1 of European Patent specification No. 322 034.

Description I: 3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine hydrogen oxalate

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Prepared according to Example 4 of European Patent specification No. 322 034.

Description J: Exo-3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane hydrogen oxalate

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Prepared according to Example 20 of European Patent specification No. 323 864.

Description K: Exo-3-(3-Dimethylamino-1,2,4-thiadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane oxalate

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Prepared according to Example 33 of European Patent specification No. 307 142.

Description L: Exo-3-(3-Isopropyl-1,2,4-thiadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane hydrogen oxalate

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Prepared according to Example 42 of European Patent specification No. 307 142.

Description M: 3-(3-Carboxamido-1,2,4-oxadiazol-5-yl)quinuclidine hydrochloride

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Prepared according to the procedure described in J. Med. Chem., 1990, 33, 1128-1138.

Description N: Exo-3-(3-Isopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane hydrochloride

Prepared according to Example 25 of European Patent specification No. 323 864.

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# EXAMPLE 1

(3R,4R)-3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane. Hydrochloride

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(3S,4R)-Ethyl-1-azabicyclo[2.2.1]heptane-3-carboxylate hydrogen oxalate (61.7g, 0.24mol) in H<sub>2</sub>O (200mL) was cooled in an ice bath, Na<sub>2</sub>CO<sub>3</sub> (38g, 0.36mol) added and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 x 250mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give the free base as a colourless oil (38.2g, 94%). To a stirred solution of cyclopropyl carboxamide oxime (22.6g, 0.226mol) in dry

THF (500mL) was added 4A molecular sieves (40g). After 0.5h, NaH(9.9g of a 55% dispersion in oil, 0.226mol) was added under a nitrogen atmosphere in portions over 40 min. After addition was complete, the mixture was heated at 50 °C (oil bath temperature) for 1h. A solution of the ester free base (19.1g, 0.113mol, obtained above) in dry THF (200mL) was added and the mixture heated under reflux for 3h. After cooling, H<sub>2</sub>O (100mL) was added and the mixture stirred for a further 15 min before filtering. The filtrate was evaporated in vacuo to remove most of the THF and the crude product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (5 x 250mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) then evaporated to give a yellow oil (25.1g) which was combined with a similar quantity from an identical reaction (total 49.3g). Column chromatography on neutral alumina (ICN Neutral Alumina, Grade 3; 2.2Kg) using CH<sub>2</sub>Cl<sub>2</sub>/MeOH (100:1) gave pure *exo*-(3R,4R) product as a pale yellow oil (18.05g, R<sub>t</sub> 10.12 min (>99%), BP10 Capillary GC column, 170 °C isothermal). Mixed fractions were also obtained (~ 1:1 *exo/endo*, 13.25g) and this material was re-equilibrated under thermodynamic conditions using NaOMe (4.8g; 1.5 equivalents) in MeOH (100mL) at reflux for 2h. The mixture was evaporated and partitioned between H<sub>2</sub>O (40mL) and CH<sub>2</sub>Cl<sub>2</sub> (100mL). The organic layer was separated and the aqueous re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100mL). The combined organic extracts were dried and evaporated to give a pale yellow oil (13.0g; ~ 5:1, *exo/endo*) to afford a further supply of pure *exo* isomer (7.8g) after column chromatography on neutral alumina (total yield, 25.85g). This material in Et<sub>2</sub>O (180mL) containing iPA (18mL) was filtered and cooled (ice bath) and then treated with saturated ethereal HCl. After ageing for 0.5h at 5 °C, the crude salt was collected (24.4g) and recrystallised twice from iPA (60mL each time) to afford the title compound as a white crystalline solid (18.0g; 31%), m.p. 169-170 °C; Found: C, 54.65; H, 6.67; N, 17.32; Cl, 14.76. C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O.HCl requires C, 54.66; H, 6.67; N, 17.38; Cl, 14.67%; R<sub>t</sub> 0.62 in CH<sub>2</sub>Cl<sub>2</sub>/MeOH (50:1) on alumina plates; [α]<sub>D</sub><sup>22</sup> -0.30° (c=1.0, MeOH); [α]<sub>D</sub><sup>22</sup> -17.4° (c=1.0, CH<sub>2</sub>Cl<sub>2</sub>); HPLC, chemical purity: R<sub>t</sub> 6.56 min (99.9%) at λ = 210nm on a Spherisorb ODS2 column (250 x 4.6mm), 10% MeCN in 50mM KH<sub>2</sub>PO<sub>4</sub>, 0.2% TEA, pH = 2.5 with H<sub>3</sub>PO<sub>4</sub>, flow rate 1mL/min; HPLC, enantiomeric purity: R<sub>t</sub> 7.06 min (> 99%) at λ = 205nm on an Enantiopac column, 5mM K<sub>2</sub>HPO<sub>4</sub>, 0.5mM t-butylidihydrogen ammonium phosphate, pH = 7.5 with H<sub>3</sub>PO<sub>4</sub>, flow rate 0.3mL/min; MS, m/z 205 M<sup>+</sup> of free base; IR ν<sub>max</sub>(nujol) 2800-2400 (NH<sup>+</sup>), 1580 cm<sup>-1</sup>(C=N); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 0.95-1.02 (2H, m, cyclopropyl-CH<sub>2</sub>), 1.11-1.21 (2H, m, cyclopropyl-CH<sub>2</sub>), 1.96-2.05 (1H, m, 5-CH), 2.08-2.16 (1H, m, cyclopropyl-CH), 2.23-2.33 (1H, m, 5-CH), 3.30-3.46 (4H, m, 4-CH, 6-CH, 7-CH<sub>2</sub>), 3.50-3.60 (1H, m, 6-CH) and 3.71-3.87 (3H, m, 2-CH<sub>2</sub> and 3-CH).

## EXAMPLE 2

### Exo 3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane Hydrochloride

N,N-Dimethyl-hydroxyguandine hydrochloride (1.04g, 0.0074mol) and 4A molecular sieves (5g) were stirred in anhydrous tetrahydrofuran (40mL) under a nitrogen atmosphere for 0.5hour. Sodium hydride (0.34g of an 80% oil dispersion, 0.012mol) was added and after the initial evolution of hydrogen the mixture was stirred at 75 °C for 1.5 hours. *Exo* Methyl-1-azabicyclo[2.2.1]heptane-3-carboxylate (0.46g, 0.003mol, J.C.S. Chem. Commun., 1988, 1618) in a minimum volume of anhydrous tetrahydrofuran was added and the mixture stirred with heating under reflux for 3 hours. The mixture was poured into water (15mL) and dichloromethane (50mL) was added. The organic layer was separated and the aqueous re-extracted with dichloromethane.

The combined organics were dried (sodium sulphate), filtered, then evaporated to give a yellow oil (0.39g) which was purified by column chromatography on silica by elution with dichloromethane/methanol (93:7) to yield the title compound free base as an oil.

The hydrochloride salt had mp 164-168 °C (propan-2-ol/diethyl ether). Mass Spectrum, m/z 208 for M<sup>+</sup> - (of free base); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 1.95-2.02 (1H, m) and 2.22-2.32 (1H, m, 5-CH<sub>2</sub>); 2.98 (6H, s, 2 x CH<sub>3</sub>); 3.29-3.78 (7H, m, 2-CH<sub>2</sub>, 4-CH, 6-CH<sub>2</sub> and 7-CH<sub>2</sub>); 3.83-3.89 (1H, m, 3-CH). (Found: C, 48.31; H, 6.96; N, 22.76. C<sub>10</sub>H<sub>16</sub>H<sub>4</sub>O. HCl 0.2H<sub>2</sub>O requires C, 48.37; H, 7.06; N, 22.56%).

## EXAMPLE 3

### 3-(3-Methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride

a) 1-t-Butyloxycarbonyl-3-(3-methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

N-Methyl-hydroxyguanidine sulphate (17.0g, 0.061mol) was stirred with 4A molecular sieves (20g) in ethanol (80mL) under a nitrogen atmosphere for 2 hours. Sodium (2.8g, 0.122mol) was added in portions

then the mixture was stirred at 50 °C for 1 hour. A solution of methyl 1-t-butyloxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylate (3.0g, 0.012mol) in ethanol (40mL) was added and the reaction mixture was stirred whilst heating under reflux for 4 hours. The mixture was cooled, filtered, evaporated to dryness. The residue was dissolved in tetrahydrofuran (40mL), treated with potassium t-butoxide (1.35g, 0.012mol) and stirred for 3 hours. Water (50mL) was added and the mixture extracted with dichloromethane (5 x 50mL). The combined organics were dried (sodium sulphate) then evaporated to dryness to give a yellow gum which was purified by column chromatography on silica using dichloromethane/methanol (80:1) to afford the product as a pale yellow gum (1.10g, 33%). (HRMS, Found:  $M^+$ , 280.1530,  $C_{13}H_{20}N_4O_3$  requires  $M$ , 280.1535). (Found: C, 54.70; H, 7.29; N, 18.91.  $C_{13}H_{20}N_4O_3$  requires C, 55.70; H, 7.19, N, 19.99%).

b) 3-(3-Methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride

The foregoing oxadiazole (1.05g, 0.0037mol) was stirred with trifluoroacetic acid (1.7mL, 0.022mol) in dichloromethane (10mL) for 18 hours.

The hydrochloride salt had mp 231-233 °C (propan-2-ol/methanol).  $R_f$  = 0.56 in dichloromethane/methanol (9:1) on alumina plates. Mass Spectrum,  $m/z$  179 for  $(M-H)^+$  of free base; IR (nujol)  $\nu_{max}$  3310(NH), 2800-2500(NH<sup>+</sup>), 1665cm<sup>-1</sup> (C=C, C=N); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O)  $\delta$  2.70-2.75 (2H, m, 5-CH<sub>2</sub>); 2.84 (3H, s, CH<sub>3</sub>); 3.45 (2H, dd, J = 6Hz, 6-CH<sub>2</sub>); 4.10 (2H, dd, J = 2Hz, 2-CH<sub>2</sub>); 7.23-7.25 (1H, m, 4-CH). (Found: C, 44.34; H, 6.16; N, 25.30.  $C_8H_{12}N_4O \cdot HCl$  requires C, 44.35; H, 6.05; N, 25.86%).

EXAMPLE 4

3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride

N,N-Dimethyl-hydroxyguanidine hydrochloride (7.40g, 0.053mol) was stirred with 4A molecular sieves (25g) in anhydrous tetrahydrofuran (150mL) for 0.5 hour under a nitrogen atmosphere. Sodium hydride (4.8g of a 55% oil dispersion, 0.11mol) was added in portions then the mixture was heated at 50 °C for 1 hour. A solution of 3-methoxycarbonyl-1-vinyloxycarbonyl-1,2,5,6-tetrahydropyridine (5.0g, 0.024mol) in anhydrous tetrahydrofuran (50mL) was added and the mixture stirred whilst heating under reflux for 2 hours. The mixture was cooled, water (100mL) and dichloromethane (250mL) were added then filtered. The organic layer was separated and the aqueous re-extracted with dichloromethane (100mL). The combined organics were dried (sodium sulphate) then evaporated to give an orange oil (6.20g). The product was purified by column chromatography on neutral alumina (Grade 3) using dichloromethane/methanol (120:1) to afford the title compound free base as a yellow oil (3.15g, 68%). The hydrochloride salt had mp 200-201 °C (propan-2-ol).  $R_f$  = 0.78 in dichloromethane/methanol (9:1) on alumina plates. Mass Spectrum,  $m/z$  194 for  $M^+$  of free base; IR (nujol)  $\nu_{max}$  2800-2300 (NH<sup>+</sup>), 1665cm<sup>-1</sup> (C=C, C=N); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O)  $\delta$  2.70-2.76 (2H, m, 5-CH<sub>2</sub>); 3.00 (6H, s, 2 x CH<sub>3</sub>); 3.46 (2H, dd, J = 6Hz, 6-CH<sub>2</sub>); 4.11-4.14 (2H, m, 2-CH<sub>2</sub>); 7.23-7.27 (1H, m, 4-CH). (Found: C, 46.85; H, 6.57; N, 24.15.  $C_9H_{14}N_4O \cdot HCl$  requires C, 46.86; H, 6.55; N, 24.29%).

EXAMPLE 5

3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride

The title compound free base (1.50g, 55%) was obtained from arecoline (2.0g, 0.013mol) and N,N-Dimethylhydroxyguanidine hydrochloride (3.63g, 0.026mol) in a similar manner as described for Example 4. The hydrochloride salt had mp 202-203 °C (propan-2-ol/methanol). (Found: C, 48.92; H, 6.94; N, 22.75.  $C_{10}H_{16}N_4O \cdot HCl$  requires C, 49.08; H, 7.00; N, 22.89%).

EXAMPLE 6

3-(3-Dipropargylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

a) 1-t-Butyloxycarbonyl-3-(3-amino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

The title compound (1.72g, 16%) was prepared from hydroxyguanidine hemisulphate hemihydrate (55.90g, 0.42mol) and methyl 1-t-butyloxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10.0g, 0.041mol). Mass Spectrum,  $m/z$  266 for  $M^+$ .

b) 1-t-Butyloxycarbonyl-3-(3-dipropargyl amino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

Sodium hydride (65mg of a 55% oil dispersion, 0.0015mol) was added to a stirred solution of the foregoing amino-oxadiazole (350mg, 0.0013mol) in anhydrous tetrahydrofuran (12mL) under a nitrogen atmosphere. A solution of propargyl bromide (0.11mL, 0.0015mol) in anhydrous tetrahydrofuran (3mL) was added dropwise and the mixture was stirred at room temperature for 72 hours. Water (30mL) was added and the mixture extracted with dichloromethane (20mL). The organic layer was separated and the aqueous further extracted with dichloromethane (20mL). The combined organics were washed with water (20mL), dried (sodium sulphate) then evaporated to give a gum (480mg) which was purified by column chromatography on silica using dichloromethane/methanol (100:1) to afford the title compound as a yellow oil (150mg, 38%). Mass Spectrum,  $m/z$  344 for  $(M+2H)^+$ ;  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  1.49 (9H, s, 3 x  $CH_3$ ); 2.26-2.28 (2H, m, 2 x  $C\equiv CH$ ); 2.34-2.42 (2H, m, 5- $CH_2$ ); 3.55 (2H, dd,  $J = 6Hz$ , 6- $CH_2$ ); 4.24-4.34 (6H, m, 2- $CH_2$ , 2 x  $CH_2C\equiv C$ ); 7.06-7.10 (1H, m, 4-CH).

c) 3-(3-Dipropargylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

The foregoing oxadiazole (135mg, 0.00039mol) was stirred with trifluoroacetic acid (0.18mL, 0.0024mol) in dichloromethane (6mL) for 24 hours. The hydrogen oxalate salt had mp 134-135 °C (propan-2-ol).  $R_f = 0.78$  in dichloromethane/methanol (9:1) on alumina plates. Mass Spectrum,  $m/z$  242 for  $M^+$  of free base. (Found: C, 53.87; H, 4.90; N, 16.52.  $C_{13}H_{14}N_4O$ .  $C_2H_2O_4$  requires C, 54.21; H, 4.85; N, 16.86%).

EXAMPLE 71-Ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride

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a) 3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

The title compound (5.20g, 66%) was obtained from 3-methoxycarbonyl-1-vinyloxycarbonyl-1,2,5,6-tetrahydropyridine (10g, 0.047mol) and acetamide oxime (6.95g, 0.094mol). Mass Spectrum,  $m/z$  164 for  $(M-H)^+$ .

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b) 1-Ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride

Sodium hydride (280mg of a 55% oil dispersion, 0.0064mol) was added to a stirred solution of the foregoing oxadiazole (1.05g, 0.0064mol) in anhydrous tetrahydrofuran (10mL) under a nitrogen atmosphere. After 20 minutes a solution of iodoethane (0.51mL, 0.0064mol) in anhydrous tetrahydrofuran (5mL) was added dropwise. After stirring at room temperature for 8 hours the mixture was filtered then evaporated to dryness *in vacuo*. The residue was purified by column chromatography on neutral alumina (Grade 3) using dichloromethane/petroleum ether (40-60) (3:1) to afford the title compound free base as a colourless oil (0.51g, 41%). The hydrochloride salt had mp 157-158 °C (methanol/diethyl ether).  $R_f = 0.80$  in dichloromethane/methanol (9:1) on alumina plates. Mass Spectrum,  $m/z$  192 for  $(M-H)^+$  of free base; IR (nujol)  $\nu_{max}$  2600-2200 ( $NH^+$ ), 1660 $cm^{-1}$  ( $C=C$ ,  $C=N$ );  $^1H$  NMR (360MHz,  $D_2O$ )  $\delta$  1.42 (3H, t,  $J = 7Hz$ ,  $CH_2CH_3$ ); 2.42 (3H, s, oxadiazole- $CH_3$ ); 2.78-2.84 (2H, m, 5- $CH_2$ ); 3.40 (2H, q,  $J = 7Hz$ ,  $CH_2CH_3$ ); 3.44-3.64 (2H, m, 6- $CH_2$ ); 4.10-4.30 (2H, m, 2- $CH_2$ ); 7.30-7.33 (1H, m, 4-CH). (Found: C, 48.76; H, 6.62; N, 16.98.  $C_{10}H_{15}N_3O$ . HCl.  $H_2O$  requires C, 48.49; H, 7.32; N, 16.96%).

45

EXAMPLE 8Anti 6-(3-Ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.2]octane Hydrochloride

50

a) Anti 2-t-Butyloxycarbonyl-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.2]octane

The title compound (0.75g, 22%) was obtained from propionamide oxime (2.11g, 0.023mol) and anti methyl 2-t-butyloxycarbonyl-2-azabicyclo[2.2.2]octane-6-carboxylate (3.0g, 0.011mol, EPA 307142)

55

b) Anti 6-(3-Ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.2]octane Hydrochloride

The foregoing oxadiazole (0.703g, 0.00229mol) was stirred with trifluoroacetic acid (3.53mL, 0.046mol) in

dichloromethane (8mL) for 3 hours. The hydrochloride salt had mp 166-167 °C (propan-2-ol).  $R_f$  = 0.33 in dichloromethane/methanol (20:1) on silica plates. Mass Spectrum,  $m/z$  208 for  $(M+H)^+$  of free base. (Found: C, 54.27; H, 7.39; N, 17.27.  $C_{11}H_{17}N_3O \cdot HCl$  requires C, 54.21; H, 7.44; N, 17.24%).

## 5 EXAMPLE 9

### (-)-Anti 6-(3-Ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.2]octane Hydrochloride

(-)-Dibenzoyltartaric acid (4.09g, 0.0114mol) in ethanol (25mL) was added to a solution of racemic anti  
 10 6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.2]octane (9.47g, 0.0457mol, Example 10) in ethanol (15mL). The crystals were collected and the mother liquors evaporated to dryness then the free base liberated. This free base was treated with (+)-dibenzoyl tartaric acid (3.48g, 0.0097mol) in ethanol (35mL). The crystals were collected and recrystallised once from propan-2-ol then twice from ethanol to afford the (+)-DBT salt as crystalline solid (0.83g), mp 171-172 °C. The hydrochloride salt had mp 187-188 °C.  $[\alpha]_D^{22}$  °C - 52.4 ° (c  
 15 = 1, methanol). (Found: C, 53.98; H, 7.41; N, 17.03.  $C_{11}H_{17}N_3O \cdot HCl$  requires C, 54.21; H, 7.44; N, 17.24%).

## EXAMPLE 10

### 20 3-(3-Ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Trifluoroacetate

#### a) 1-t-Butyloxycarbonyl-3-(3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

The title compound (8.0g, 45%) was prepared from 3-hydroxypropionamide oxime (15.90g, 0.15mol),  
 25 methyl 1-t-butyloxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylate (14.48g, 0.06mol) and sodium (3.45g, 0.15mol) in ethanol (550mL). Mass spectrum,  $m/z$  296  $(M+H)^+$ .

#### b) 1-t-Butyloxycarbonyl-3-(3-(2-methanesulphonyloxyethyl)-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

30 The title compound (8.0g, 93%) was prepared from the foregoing hydroxy compound (6.76g, 23mmol), triethylamine (3.33mL, 24mmol) and methanesulphonyl chloride (1.8mL, 23mmol) in dichloromethane (50mL). Mass spectrum,  $Cl^+$ ,  $m/z$  318 (McLafferty rearrangement ion).

#### c) 1-t-Butyloxycarbonyl-3-(3-ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

35 1,8-Diazabicyclo[5.4.0]undec-7-ene (3.1mL, 21mmol) was added to a solution of the foregoing mesylate (7.70g, 21mmol) in toluene (30mL) and heated at 65 °C for 4.5 hours. After cooling water (30mL) was added, the organic layer separated, dried then evaporated. The crude product was purified by column chromatography on silica using dichloromethane/methanol (200:1) to afford the title compound as a  
 40 colourless solid (4.44g, 76%), mp 81-82 °C.  $R_f$  0.58 in ethyl acetate/petroleum ether (60-80) (1:1) on silica plates. Mass spectrum,  $m/z$  221 (McLafferty rearrangement ion).

#### d) 3(3-Ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Trifluoroacetate

45 Trifluoroacetic acid (22mL, 280mmol) was added to a cooled (4 °C) solution of the foregoing olefin (4.0g, 14mmol) in dichloromethane (20mL). After 2 hours at room temperature the mixture was evaporated to dryness and the title compound recrystallised from propan-2-ol (2.95g, 72%), mp 92-94 °C. Mass spectrum,  $m/z$  177 for  $M^+$  of free base. (Found: C, 45.39; H, 4.21; N, 14.30.  $C_9H_{11}N_3O \cdot CF_3CO_2H$  requires C, 45.37; H, 4.15; N, 14.43%).

50

## EXAMPLE 11

### 3-(3-Ethyl-1,2,4-oxadiazol-5-yl)piperidine Hydrochloride

55 The title compound free base (1.25g, 73%) was obtained from ethyl nipecotate (1.50g, 9.5mmol), propionamide oxime (1.26g, 14.3mmol) and sodium hydride (0.624g of a 55% oil dispersion, 14.3mmol) in anhydrous tetrahydrofuran (85mL). The hydrochloride salt had mp 120-121 °C (propan-2-ol/diethyl ether).  $R_f$  0.77 in dichloromethane/methanol (9:1) on alumina plates. Mass spectrum,  $m/z$  182 for  $(M+H)^+$  of free

base;  $^1\text{H}$  NMR (360MHz,  $\text{D}_2\text{O}$ )  $\delta$  1.28 (3H, t,  $J = 7.5\text{Hz}$ ,  $\text{CH}_3$ ); 1.87-2.08 (3H, m) and 2.28-3.55 (1H, m, 4- $\text{CH}_2$  and 5- $\text{CH}_2$ ); 2.78 (2H, q,  $J = 7.5\text{Hz}$ ,  $\text{CH}_2$ ); 3.08-3.16 (1H, m, one of 6- $\text{CH}_2$ ); 3.39 (1H, dd,  $J = 10, 13\text{Hz}$ , one of 2- $\text{CH}_2$ ); 3.40-3.47 (1H, m, one of 6- $\text{CH}_2$ ); 3.56-3.64 (1H, m, 3-CH); 3.76 (1H, dd,  $J = 4, 13\text{Hz}$ , one of 2- $\text{CH}_2$ ). (Found: C, 49.54; H, 7.30; N, 19.15.  $\text{C}_9\text{H}_{15}\text{N}_3\text{O} \cdot \text{HCl}$  requires C, 49.65; H, 7.41; N, 19.30%).

5

EXAMPLE 123-(3-t-Butylaminocarbonylamino-1,2,4-oxadiazol-5-yl)quinuclidine Hydrochloride

10 The title compound free base (0.58g, 73%) was prepared using 3-(3-amino-1,2,4-oxadiazol-5-yl)-quinuclidine (0.52g, 2.7mmol) and t-butyliisocyanate (1mL, 8.7mmol) in pyridine (10mL) at  $100^\circ\text{C}$  for 24 hours. The hydrochloride salt had mp  $206^\circ\text{C}$  (methanol/diethyl ether).  $R_f$  0.50 in dichloromethane/methanol (20:1) on alumina plates. Mass spectrum,  $m/z$  293 for  $\text{M}^+$  of free base. (Found: C, 49.40; H, 7.13; N, 20.73.  $\text{C}_{14}\text{H}_{23}\text{N}_5\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$  requires C, 49.62; H, 7.44; N, 20.67%).

15

EXAMPLE 133-(3-Ethyl-1,2,4-oxadiazol-5-yl)quinuclidine Hydrogen Oxalate

20 The title compound free base (17g, 77%) was prepared from methyl quinuclidine-3-carboxylate (18.0g, 0.11mol), propionamide oxime (14g, 0.16mol) and sodium hydride (7g of a 55% oil dispersion, 0.16mol) in anhydrous tetrahydrofuran (350mL). The hydrogen oxalate salt had mp  $113-115^\circ\text{C}$  (propan-2-ol).  $R_f$  0.3 in dichloromethane/methanol (50:1) on alumina plates. (Found: C, 52.25; H, 6.41; N, 14.07.  $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O} \cdot \text{C}_2\text{H}_2\text{O}_4$  requires C, 52.52; H, 6.44; N, 14.13%).

25

EXAMPLE 14Exo-3-(3-n-Pentyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane p-Toluene Sulphonate

30 The title compound free base (0.59g, 35%) was obtained from endo ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate (1.2g, 7.1mmol), n-pentylcarboxamide oxime (1.85g, 1.4mmol) and sodium hydride (0.62g of a 55% oil dispersion, 1.4mmol) in anhydrous tetrahydrofuran (110mL). The p-toluene sulphonate salt had mp  $128-129^\circ\text{C}$  (propan-2-ol/ethyl acetate).  $R_f$  0.5 in dichloromethane/methanol (99:1) on alumina. Mass spectrum,  $m/z$  236 for  $(\text{M} + \text{H})^+$  of free base. (Found: C, 58.94; H, 7.21; N, 10.26.  $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O} \cdot \text{C}_7\text{H}_8\text{O}_3\text{S}$  requires C, 58.94; H, 7.17; N, 10.31%).

35

EXAMPLE 15Exo-3-(3-(3-Methylbut-1-yl)-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane p-Toluene Sulphonate

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The title compound free base (0.625g, 38%) was obtained from endo ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate (1.2g, 7.1mmol), 3-methylbut-1-yl carboxamide oxime (1.85g, 1.4mmol) and sodium hydride (0.62g of a 55% oil dispersion, 1.4mmol) in anhydrous tetrahydrofuran (110mL). The p-toluene sulphonate salt had mp  $122-123^\circ\text{C}$  (propan-2-ol/ethyl acetate).  $R_f$  0.5 in dichloromethane/methanol (99:1) on alumina plates. Mass spectrum,  $m/z$  235 for  $\text{M}^+$  of free base. (Found: C, 57.54; H, 6.8; N, 10.03.  $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O} \cdot \text{C}_7\text{H}_8\text{O}_3\text{S} \cdot 0.5\text{H}_2\text{O}$  requires C, 57.67; H, 7.2; N, 10.08%).

45

EXAMPLE 1650 Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine hydrochloride (3R,4R)-3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane. Hydrochloride Exo 3-(3-Dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane Hydrochloride

55

TABLE FOR DOSES CONTAINING FROM 1-25MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

TABLE FOR DOSES CONTAINING FROM 26-100MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	26.0	50.0	100.0
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

#### EXAMPLE 17

##### Eye Drops

Solution compositions for topical administration containing 1.0 mg of the compounds of the Descriptions and Examples are prepared as illustrated below:

The pharmaceutically acceptable

salt of the active compound

0.5%

Benzalkonium chloride solution

0.02% v/v

Disodium edetate

0.05%

NaCl

0.8%

Water for injections

to 100%

Compound, disodium edetate, sodium chloride and benzalkonium chloride are added to and admixed with water. The final formulation is diluted to volume. The formulation is rendered sterile by appropriate means, such as starting the preparation procedure with sterile components and proceeding under sterile conditions, irradiating or autoclaving the finished formulation, or the like.

#### EXAMPLE 18

##### Ophthalmic Inserts

Ophthalmic inserts containing 1.0 mg of the following compounds are prepared as illustrated below: 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine hydrochloride; (3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane hydrochloride; exo3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane hydrochloride.



Active compound	1 mg
Hydroxypropylcellulose q.s.	12 mg

- 5 Ophthalmic inserts are manufactured from compression moulded films which are prepared on a Carver Press by subjecting the powdered mixture of the above ingredients to a compressional force of 12,000 lbs (gauge) at 300 ° F for one to four minutes. The film is cooled under pressure by having cold water circulate in the platen. Ophthalmic inserts are then individually cut from the film with a rod-shaped punch. Each insert is placed into a vial, which is then placed in a humidity cabinet (88% R.H. at 30 ° C) for two to four days.
- 10 After removal from the humidity cabinet, the vials are stoppered and then capped. The vials containing the hydrate insert are then autoclaved at 250 ° F for  $\frac{1}{2}$  hour.

#### METHOD FOR BIOLOGICAL ACTIVITY

- 15 Male or female African Green monkeys (2.0 - 4.5 kg) were fasted following their afternoon feeding on the day prior to the experiment. The monkeys were anaesthetised in their cages with approximately 10mg/kg i.m. ketamine HCl (Vetalar or Ketaset). Once sedated, the animals were restrained in monkey chairs and brought to the laboratory. One drop of 0.5% proparacaine HCl (Ophthetic) was instilled into each eye. After 30 seconds, intraocular pressure (IOP) determinations were taken in each eye (control or "0" time reading)
- 20 using a Digilab Modular One Pneuma Tonometer. Both eyes were then flushed with saline. Vehicle or test agent (0.0005 - 2.0%) was administered (25  $\mu$ l) into the cul-de-sac of both eyes and the IOP was determined at 0.5 and 1.0 hour and at hourly intervals thereafter for up to 5 hours and compared to the control IOP. For ocular instillation, 0.5% hydroxyethylcellulose (HEC) was employed as the vehicle. Supplemental doses of 10mg or more/animal i.m. ketamine HCl were given 3-5 minutes prior to IOP
- 25 determinations. Proparacaine HCl (0.5%) (one drop/eye) was also instilled immediately prior to IOP determinations. Following the final IOP determination, both eyes were flushed liberally with saline and a sterile ophthalmic ointment (Ilotycin, erythromycin, 5mg/gm) was applied. Animals were allowed to recover in their cages and a light meal was provided. At least 2 days separated individual intraocular pressure experiments.
- 30 Pupil diameter was measured under standard laboratory lighting conditions using a millimeter ruler. ["Vetalar," "Ketaset", "Ophthetic", "Digilab Modular One" and "Ilotycin" are all trade marks.]

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BIOLOGICAL ACTIVITY

5	Compound of	Concentration	Change in IOP <sup>a</sup>
10	Descrip- tion A	0.0005%	-6
15	Descrip- tion B	0.005%	-5
20	Descrip- tion C	0.05%	-5
25	Descrip- tion D	0.05%	-3
30	Descrip- tion E	0.05%	-3
35	Descrip- tion F	0.5%	-2
40	Descrip- tion G	1.5%	-4.5

45

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	Description H	2.0%	-1.5
5	Description I	2.0%	-4.5
10	Description J	0.05%	-3
15	Description K	0.5%	-3.5
20	Description L	0.5%	-2.5
25	Description M	0.5%	-3.5
30	Description N	0.5%	-2.5
35	Example 1	0.05%	-5
40	Example 2	0.10%	-5
45	Example 3	2.0%	-5
50	Example 4	0.005%	-4
55			

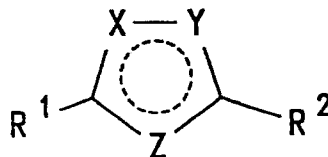
EP 0 459 568 A2

5	Example 5	0.005%	-2
10	Example 6	0.5%	-3
15	Example 7	0.05%	-2
20	Example 8	2.0%	-5
25	Example 9	2.0%	-3
30	Example 10	2.0%	-3.5
35	Example 11	0.5%	-3
40	Example 12	0.05%	-3
45	Example 13	2.0%	-3
50	Example 14	2.0%	-2
55	Example 15	0.5%	-2

55 FOOTNOTE: a, Maximum mm Hg change in intraocular pressure

## Claims

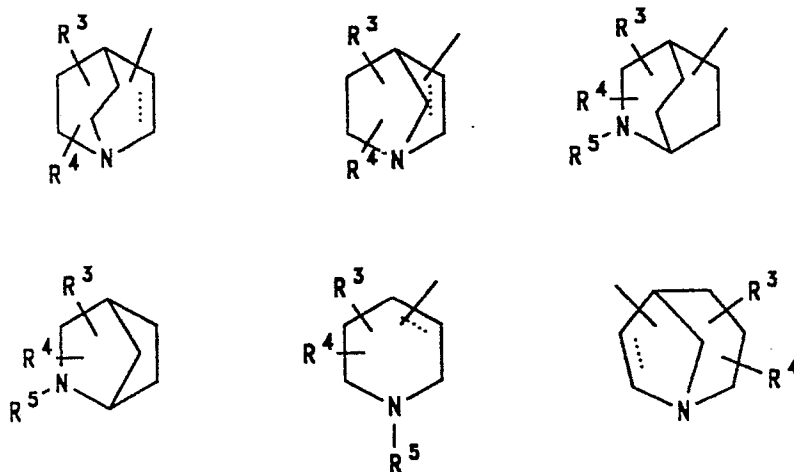
1. The use of a compound of formula (I):



( I )

or a salt or prodrug thereof; wherein one of X, Y, or Z is an oxygen or sulphur atom and the other two are nitrogen atoms, and the dotted circle represents two double bonds thus forming a 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole or 1,2,4-thiadiazole nucleus;

R<sup>1</sup> represents a non-aromatic azacyclic or azabicyclic ring system selected from



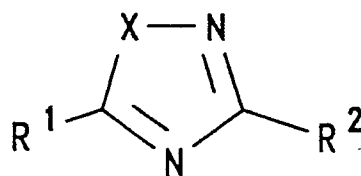
wherein the broken line represents an optional chemical bond;

the substituents R<sup>3</sup> and R<sup>4</sup> may be present at any position, including the point of attachment to the oxa- or thia-diazole ring, and independently represent hydrogen, C<sub>1-4</sub> alkyl, halo, C<sub>1-4</sub> alkoxy, hydroxy or carboxy, or R<sup>3</sup> and R<sup>4</sup> together represent carbonyl;

the group R<sup>5</sup> represents hydrogen or C<sub>1-4</sub> alkyl; and

R<sup>2</sup> represents hydrogen, C<sub>1-8</sub> alkyl optionally substituted by hydroxy or fluoro, C<sub>2-8</sub> alkenyl, OR<sup>7</sup>, SR<sup>7</sup>, NR<sup>7</sup>R<sup>8</sup>, CN, CO<sub>2</sub>R<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup> or NHCONHR<sup>9</sup> where R<sup>9</sup> is C<sub>1-4</sub> alkyl; wherein R<sup>7</sup> and R<sup>8</sup> independently represent hydrogen or saturated or unsaturated C<sub>1-4</sub> alkyl provided that, when R<sup>7</sup> and R<sup>8</sup> in NR<sup>7</sup>R<sup>8</sup> are both hydrogen, at least one of R<sup>3</sup> and R<sup>4</sup> is C<sub>1-4</sub> alkyl for the manufacture of a medicament for use in reducing intraocular pressure or the treatment of glaucoma.

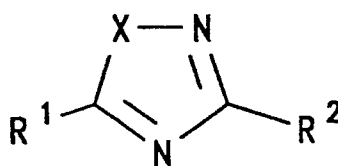
2. The use as claimed in claim 1 wherein the compound is of formula (II):



10 ( I I )

15 wherein R<sup>1</sup>, R<sup>2</sup> and X are as defined for formula (I), or a salt or prodrug thereof, for the manufacture of a medicament for use in reducing intraocular pressure or the treatment of glaucoma.

- 20 3. The use as claimed in claim 1 or claim 2 wherein R<sup>1</sup> is 1,2,5,6-tetrahydropyridinyl optionally substituted on the ring nitrogen with methyl or ethyl, 1-azabicyclo[2.2.1]heptanyl, 2-azabicyclo[2.2.2]octanyl or quinuclidinyl.
4. The use as claimed in any of claims 1 to 3 wherein R<sup>3</sup> and R<sup>4</sup> are selected from hydrogen, hydroxy and C<sub>1-4</sub> alkyl.
- 25 5. The use as claimed in any of claims 1 to 4 wherein R<sup>5</sup> represents hydrogen, methyl, or ethyl.
6. The use as claimed in any of claims 1 to 5 wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl, optionally substituted by OH, F, or NR<sup>7</sup>R<sup>8</sup> when R<sup>7</sup> is hydrogen, or saturated or unsaturated C<sub>1-3</sub> alkyl, and R<sup>8</sup> is saturated or unsaturated C<sub>1-3</sub> alkyl.
- 30 7. The use as claimed in claim 6 wherein R<sup>2</sup> is methyl, ethyl, cyclopropyl, methylamino, dimethylamino or dipropargylamino.
8. The use as claimed in claim 1 wherein the compound is of formula (III):



40 ( I I I )

45 wherein R<sup>1</sup> is 1,2,5,6-tetrahydropyridyl (optionally substituted on the ring nitrogen with methyl or ethyl), 1-azabicyclo[2.2.1]heptanyl, 2-azabicyclo[2.2.2]octanyl (isoquinuclidinyl), quinuclidinyl or piperidyl;

R<sup>3</sup> and R<sup>4</sup> are selected from hydrogen, hydroxy and C<sub>1-4</sub> alkyl (preferred is when R<sup>3</sup> is hydrogen);

50 R<sup>5</sup> is hydrogen, methyl or ethyl;

R<sup>2</sup> is C<sub>1-8</sub> alkyl, preferably C<sub>1-5</sub> alkyl, optionally substituted by OH or F, C<sub>2-8</sub> alkenyl, preferably ethenyl, NR<sup>7</sup>R<sup>8</sup> or CONR<sup>7</sup>R<sup>8</sup> when R<sup>7</sup> is hydrogen, or saturated or unsaturated C<sub>1-3</sub> alkyl, and R<sup>8</sup> is hydrogen or saturated or unsaturated C<sub>1-3</sub> alkyl, or NHCONHR<sup>9</sup> where R<sup>9</sup> is C<sub>1-4</sub> alkyl.

- 55 9. The use of a compound selected from:  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine;  
 Exo-3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 3-(3-methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;

- 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine;  
 3-(3-dipropargylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-ethyl-1,2,5,6-tetrahydropyridine;  
 5 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 Exo-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
 (-)-Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
 Endo-3-(3-cyclopropyl-1,2,4-thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 10 Endo-3-(3-dimethylamino-1,2,4-thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane; and  
 (3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine;  
 3-(3-methyl-1,2,4-oxadiazol-5-yl)-5-methyl-1,2,5,6-tetrahydropyridine;  
 15 3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,5-dimethyl-1,2,5,6-tetrahydropyridine;  
 Exo-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane;  
 Exo-3-(3-dimethylamino-1,2,4-thiadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane;  
 Exo-3-(3-isopropyl-1,2,4-thiadiazol-5-yl)-endo-5-hydroxy-1-azabicyclo[2.2.1]heptane;  
 3-(3-carboxamido-1,2,4-oxadiazol-5-yl)quinuclidine;  
 20 Exo-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 3-(3-ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidine;  
 3-(3-t-butylaminocarbonylamino-1,2,4-oxadiazol-5-yl)quinuclidine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)quinuclidine;  
 25 Exo-3-(3-n-pentyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 Exo-3-(3-(3-methylbut-1-yl)-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 and salts and prodrugs thereof, for the manufacture of a medicament for use in reducing intraocular  
 pressure or the treatment of glaucoma.
- 30 **10.** A compound selected from:  
 Exo-3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 3-(3-methylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-dimethylamino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine;  
 35 3-(3-dipropargylamino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-ethyl-1,2,5,6-tetrahydropyridine;  
 Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
 (-)-Anti-6-(3-ethyl-1,2,4-oxadiazol-5-yl)-2-azabicyclo-[2.2.2]octane;  
 3-(3-ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine;  
 40 3-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidine;  
 3-(3-t-butylaminocarbonylamino-1,2,4-oxadiazol-5-yl)quinuclidine;  
 3-(3-ethyl-1,2,4-oxadiazol-5-yl)quinuclidine;  
 Exo-3-(3-n-pentyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo-[2.2.1]heptane;  
 Exo-3-(3-(3-methylbut-1-yl)-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane;  
 45 and salts and prodrugs thereof.
- 11.** A pharmaceutical formulation comprising a compound as claimed in claim 10 and a pharmaceutically  
 acceptable carrier.
- 50 **12.** A pharmaceutical formulation adapted for topical administration to the eye comprising a compound of  
 formula (I) and a carrier suitable for topical administration.